REMARKS

Applicants respectfully request reconsideration of the present application.

I. Status of the Claims

Claims 11 – 36, 40 – 45, 47 – 49, and 51 – 121 are pending in this application.

Independent claims 11, 23, 35, 40, 42, 43, and 44 have been amended to recite that the dry powder nanoparticulate compositions returns to a nanoparticulate drug particle dispersion upon reconstitution in "an aqueous" liquid medium. Exemplary support for this amendment can be found in the specification at, for example, pages 8-9 (describing preparation of dry powders of aqueous nanoparticulate drug dispersions).

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Summary of the Claimed Invention

The claimed invention is directed to dry powder aerosols of nanoparticulate crystalline drugs for pulmonary and nasal delivery. All of Applicants' claims require at least the following: (1) "spherically shaped aggregates" of nanoparticulate crystalline drug and surface modifier; (2) *crystalline* drug particles; (3) component crystalline drug particles having an average particle size of less than about 1 micron; and (4) wherein the aggregates of nanoparticulate crystalline drug and surface modifier return to nanoparticulate drug particle dispersions upon reconstitution in a liquid medium. *See e.g.*, Applicants' independent claims 11, 23, 35, 40, 42, 43, and 44. *None* of the cited prior art, either alone or in combination, teaches or suggests this combination of claim elements.

III. The Office Action

A. Rejection of Claims Under 35 U.S.C. § 103(a) Over Edwards et al.

Claims 11-34, 40, 41, 45, 47, 48, 51-62, 69-96, and 111-119 remain rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Edwards et al. (U.S. Patent

No. 5,985,309) ("Edwards"). Office Action at page 2. Applicants respectfully traverse this ground for rejection.

Because Edwards fails to teach or suggest dry powder aerosols comprising: (1) "spherically shaped aggregates" of nanoparticulate drug and surface modifier; (2) crystalline drug particles; (3) component crystalline drug particles having an average particle size of less than about 1 micron; and (4) wherein the aggregates of nanoparticulate crystalline drug and surface modifier return to nanoparticulate drug particle dispersions upon reconstitution in a liquid medium, all of which are required by Applicants' claims, Edwards fails to teach or suggest Applicants' claimed invention.

1. The Examiner has Failed to Provide Motivation, Existing in the art at the Time the Claimed Invention was Made, to Modify the Particles of Edwards to Obtain "Spherically Shaped Particles," as Required by Applicants' Claims

In the previous Amendment, filed on June 24, 2004, Applicants argued that Edwards does not teach or suggest dry powder aerosols comprising "spherical aggregates" of nanoparticulate drug particles.

In response, the Examiner stated that: "it is the examiner's position that the prior art as known and expressed in Edwards teaches smooth and spherical microparticle drug for inhalation (col. 9, lin 11-21)." Office Action at page 2.

The passage cited by the Examiner states the following:

> The polymeric particles are preferably prepared by spray drying. Prior methods of spray drying, such as that disclosed in PCT WO 96/09814 by Sutton and Johnson, disclose the preparation of smooth, spherical microparticles of a water-soluble material with at least 90% of the particles possessing a mean size between 1 and 10 μm. *The method disclosed herein provides rough (non-smooth), non-spherical microparticles* that include a water-soluble material combined with a water-insoluble material. At least 90% of the particles possess a mean size between 5 and 30 μm, and a low mass or tap density (less than 0.4 g/cc).

(Emphasis added.)

Thus, the passage cited by the Examiner teaches that, in contrast to the claimed invention, the particles of Edwards are rough and non-smooth. While the Examiner points out that smooth particles were known in the prior art, *the Examiner has failed to provide motivation to modify the compositions of Edwards to obtain the claimed invention; i.e.*, to modify the rough particles of Edwards to obtain the smooth spherical particles of the claimed invention. Such motivation is required for a proper *prima facie* case of obviousness.

In fact, Edwards teaches *away* from the claimed invention, as this reference *contrasts* the "rough" particles of Edwards with the "smooth" particles known in the prior art. Specifically, Edwards teaches that "[d]ifferent properties of the particle which can contribute to the aerodynamic lightness [which is a preferred property of the Edwards' particles] include . . . the presence of irregular surface structure." Col. 5, lines 64-67, of Edwards. Moreover, the examples of Edwards teach the production of particles that are "highly porous with irregular surface shape." *See* col. 14, lines 10-15. Thus, Edwards teaches that "spherically smooth" particles, such as those encompassed by Applicants' claims, are undesirable in the context of Edwards aerosol composition.

Because Edwards does not teach or suggest each and every element of Applicants' claimed invention, the rejection should be withdrawn. Moreover, because the Examiner has failed to provide a motivation existing in the art at the time the claimed invention was made to modify the compositions of Edwards to obtain "spherically shaped aggregates", as required by the claimed invention, the rejection should be withdrawn.

2. Contrary to the Examiner's Assertion, Edwards Does not Teach or Suggest Dry Powder Aerosols Comprising Nanoparticulate Drug Particles

In the previous Amendment, filed on June 24, 2004, Applicants argued that Edwards does not teach or suggest a dry powder composition of spherical aggregates of nanoparticulate drug particles.

In response, the Examiner stated that:

> It is the examiner's position [*sic,* that] delivery of the drug, whether in the form of aggregates or single particles is a matter of choice and design and that the key issue is delivering the drug in a form that can reach the alveoli of the lung. It is the examiner's position that Edwards disclosed that nanosize drug particles in aerosol form were delivered to the alveoli of the lung (col 3, lin 330-35 and col 5, lin 30-40).

Office Action at page 3.

First, it is courteously noted that a "superior" formulation is not the standard of patentability; rather, Applicants' burden is to demonstrate that the claimed composition is not anticipated or obviated by the cited reference. Thus, if Edwards does not teach or suggest each and every element of the claimed invention, then the rejection falls – irregardless of whether the claimed formulation is "superior" in any regard to the formulation of Edwards.

Second, the examiner's opinion regarding the "key issue" of drug delivery to the lung is *irrelevant* – as the key issue is whether the cited reference teaches or suggests each and every element of the claimed invention.

Third, in contrast to the Examiner's assertion, "delivery to the alveoli of the lung" is not always the intent of an aerosol formulation. Delivery to the alveoli is only required for systemic delivery of a drug. Other types of aerosol delivery include delivery to the nasal passages and delivery to the upper pulmonary region for, *e.g.,* topical treatment for seasonal allergic rhinitis. *See e.g.,* the paragraph bridging pages 1-2 of the application.

Fourth, again in contrast to the Examiner's assertion, Edwards *does not* teach or suggest delivery of *nanoparticulate* drug particles to the pulmonary or nasal passages. In support of the Examiner's assertion, the following passages of Edwards were cited: col. 3, lines 33-35 and col. 5, lines 30-40:

> There is a need for the development of drug carriers which are capable of delivering the drug in an effective amount into the airways or the alveolar zone of the lung (col. 3, lines 33-35);

> The particles can be used for controlled systemic or local delivery of therapeutic or diagnostic agents to the respiratory tract via aerosolization. Administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example, greater than 5 μm in mean diameter. The particles can be fabricated with a rough surface texture to reduce particle agglomeration and improve flowability of the powder. The particles have improved aerosolization properties. The particle can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device (col. 5, lines 30-40).

These passages do not teach or suggest aerosol delivery of *nanoparticulate* crystalline drugs, as required by Applicants' claims.

As noted extensively by Applicants during the prosecution of this application, Edwards *does not teach or suggest aerosol delivery of nanoparticulate crystalline drug particles*. This is significant, as all of Applicants' claims recite aerosol compositions comprising crystalline drug particles having a particle size of less than about 1 micron, *i.e.,* less than about 1000 nm.

Edwards teaches that the aerosol particles have "a mean diameter of between approximately 5 μm and 30 μm" (col. 6, lines 1-7). In contrast to the claimed invention, the Edwards particles *do* not comprise component crystalline drug particles having an average particle size of less than 1 micron. This is because the process of Edwards dissolves the component drug particle in a solvent, followed by spray drying the resultant solution to form a porous powder of particles having a size of 5 to 30 microns. Such a process does not form component *nanoparticulate crystalline* drug particles.

Because Edwards does not teach or suggest each and every element of Applicants' claimed invention, the rejection should be withdrawn. Moreover, because the Examiner has failed to provide a motivation existing in the art at the time the claimed invention was made to modify the compositions of Edwards to obtain dry powder aggregates comprising *nanoparticulate crystalline* drug particles, as required by the claimed invention, the rejection should be withdrawn.

3. Edwards Does Not Teach or Suggest Particl s That Redisperse Upon Reconstitution in a Liquid Media

In the previous Amendment, filed on June 24, 2004, Applicants argued that the aggregates of nanoparticulate crystalline drug of the claimed invention are further characterized in that they redisperse into nanoparticulate drug dispersions when reconstituted in a liquid media, and that this is not taught or suggested by Edwards.

In response, the Examiner stated that:

> Examiner posits that applicant claims nanoparticles of drug and not a liquid dispersion medium. In this regard, it is noted that applicant indicates no specific liquid medium for dispersion of drug particles. Furthermore, examiner disagrees with applicant's position because the disclosures in Edwards teach that the drug particles may be fabricated with appropriate material, surface roughness, diameter and tap density for localized delivery to selected regions of the respiratory tract . . ."

Office Action at page 3.

As amended, all of the pending claims require that the "aggregates return to nanoparticulate drug particle dispersions upon reconstitution in 'an aqueous' liquid medium." The Examiner's statement that "applicant claims nanoparticles of drug and not a liquid dispersion medium" is unclear, as this claim limitation states a property of the claimed dry powder aerosols. Because the dry powder aerosols comprise component nanoparticulate crystalline drug particles, when exposed to a liquid medium, such as water, the dry powder aggregates redisperse to form a dispersion of nanoparticulate crystalline drug particles.

Second, the identity of the liquid dispersion medium is not critical to the claims; rather, the critical issue is that the dry powder aggregates redisperse in a liquid dispersion medium to form nanoparticulate crystalline drug particles. However, the claims have been amended to recite redispersion in an "aqueous" liquid medium for the sole purpose of advancing the prosecution of this case. This claim limitation is neither taught nor suggested by Edwards. The significance of this claim limitation is that the dry powder aggregates of Applicants' claimed invention must be able to redisperse for

the component nanoparticulate crystalline drug particles to come into contact with and be absorbed by nasal and lung tissues.

Because Edwards does not teach or suggest each and every element of Applicants' claimed invention, the rejection should be withdrawn. Moreover, because the Examiner has failed to provide a motivation existing in the art at the time the claimed invention was made to modify the compositions of Edwards to obtain dry powder aggregates comprising nanoparticulate crystalline drug particles, *which redisperse into nanoparticulate crystalline drug particle dispersions upon reconstitution in a liquid medium*, as required by the claimed invention, the rejection should be withdrawn.

4. The Examiner Failed to Address Applicants' Claim Limitation Requiring Crystalline Drug Particles, Which is not Taught or Suggested by Edwards

Applicants argued previously at length how the amorphous particles of Edwards are fundamentally distinct from the crystalline drug particles of the claimed invention. This argument was not addressed by the Examiner in the Office Action dated January 14, 1004.

All of Applicants' claims require the presence of nanoparticulate *crystalline* drug particles. Because Edwards does not teach or suggest this claim element, the rejection should be withdrawn. Moreover, because the Examiner has failed to provide a motivation existing in the art at the time the claimed invention was made to modify the compositions of Edwards to obtain dry powder aggregates comprising nanoparticulate *crystalline* drug particles, as required by the claimed invention, the rejection should be withdrawn.

B. Rejection of Claims Under 35 U.S.C. § 103(a) Over Edwards in View of Liversidge et al. (U.S. Patent No. 5,145,684)

Claims 11 – 34, 40 – 45, 47, 48, 51 – 62, 65 – 96, and 97 – 199 stand rejected as being allegedly obvious over Edwards in view of U.S. Pat. No. 5,145,684 to Liversidge et al. ("Liversidge"). Office Action at page 4. Applicants respectfully traverse this ground for rejection.

1. Applicants' Prior Arguments

In the previous Amendment, filed on June 24, 2004, Applicants argued that Liversidge does not disclose aerosol dosage forms of nanoparticulate drugs, while Edwards teaches significant difficulties that attend aerosol preparation and delivery. Consequently, given the teachings of Edwards and Liversidge, one of ordinary skill in the art would not have been able to make the claimed compositions with any reasonable expectation of success.

2. The Examiner's Response to Applicants' Arguments Fails to Address the Lack of Motivation, Present at the Time the Claimed Invention was Made, to Modify Edwards in View of Liversidge to Obtain the Claimed Invention

In response, the Examiner stated that these arguments were not persuasive because:

> the disclosure in Edwards teaches (1) incorporation of surfactants into the drug particles thereby effectively reducing the tendency of the particles to agglomerate . . . and (2) the effective delivery of the drug particles in the lung . . ."

Continuing, the Examiner concluded that:

> It is the examiner's position that overall, the disclosures in Leversidge [*sic,* Liversidge]: (a) are in the same field of endeavor as that of Edwards – nanosize drug particles that are surface modified in liquid dispersion . . . and (b) address similar problems that were raised in Edwards concerning nanosize drug delivery formulations through the respiratory tract and therefore inhalation . . ."

Office Action at page 4.

First, Liversidge and Edwards are *not* "in the same field of endeavor," as Edwards does not teach or suggest "nanosize drug particles that are surface modified in liquid dispersion." Moreover, Liversidge does not address issues related to "nanosize drug delivery formulations through the respiratory tract."

Second, the Examiner has failed to address how Liversidge would provide motivation to one of skill in the art at the time the claimed invention was made to

address the deficiencies of Edwards; namely, the failure to teach a dry powder aerosol comprising: (1) "spherically shaped aggregates" of nanoparticulate crystalline drug and surface modifier; (2) crystalline drug particles; (3) component crystalline drug particles having an average particle size of less than about 1 micron; and (4) wherein the aggregates of nanoparticulate crystalline drug and surface modifier return to nanoparticulate crystalline drug particle dispersions upon reconstitution in a liquid medium, all of which are required by Applicants' claims.

The analysis is not whether Edwards and the claimed invention both describe "effective delivery to the lung;" rather, the analysis is whether Edwards, in combination with Liversidge, teach or suggest each and every element of Applicants' claimed invention. This has not been shown.

Specifically, Edwards teaches that non-spherical, rough particles comprising drug, which are aerodynamically light and porous, are preferred. This is in contrast to the claimed invention, requiring spherically smooth particles of crystalline (i.e., solid and heavy) drug. In fact, Edwards specifically contrasts the described light and porous particles with heavier denser particles, such as those encompassed by Applicants' crystalline drug particles:

> In comparison to smaller, relatively denser particles, the larger . . . aerodynamically light particles also can potentially more successfully avoid phagocytic engulfment by alveolar macrophages and clearance from the lungs, due to size exclusion of the particles from the phagocytes' cytosolic space. . . . For particles of statistically isotropic shape, such as spheres with rough surfaces, the particle envelope volume is approximately equivalent to the volume of cytosolic space required within a macrophage for complete particle phagocytosis.
>
> Aerodynamically light particles thus are capable of a longer term release of an encapsulated agent in the lungs. Following inhalation, aerodynamically light biodegradable particles can deposit in the lungs (due to their relatively low tap density), and subsequently undergo slow degradation and drug release, without the majority of the particles being phagocytosed by alveolar macrophages. The drug can be delivered relatively slowly into the alveolar fluid, and at a controlled rate into the

> blood stream, minimizing possible toxic responses of exposed cells to an excessively high concentration of the drug.

Edwards at col. 10, lines 17-45.

Thus, Edwards specifically teaches *away* from Applicants' claimed invention, requiring spherically smooth aggregates of crystalline drug particles. The Examiner has failed to identify why one of ordinary skill in the art, at the time the claimed invention was made, would have been motivated to modify the compositions of Edwards, in a manner which is contrary to the teachings of Edwards, as allegedly suggested by Liversidge. For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

C. Rejection of Claims Under 35 U.S.C. § 103(a) Over Edwards in View of Dalby et al. (U.S. Patent No. 5,202,110)

Claims 35, 36, 49, 63, and 64 stand rejected as being allegedly obvious over Edwards in view of U.S. Pat. No. 5,985,309 to Dalby et al. ("Dalby"). Office Action at page 4. Applicants respectfully traverse this ground for rejection.

According to the Examiner, "Dalby was relied upon as teaching the propellant or aerosolized formulation for delivery of nanosize beclomethasone particles, albeit no chlorofluorocarbon was used." Office Action at page 4.

1. Summary of Dalby

Dalby is directed to formulations of beclomethasone diproprionate for aerosol delivery via a metered dose inhaler (MDI). The compositions preferably require completely dissolving beclomethasone dipropionate in a propellant blend which "assure[s] more efficient dosing with an MDI." Abstract of Dalby. Thus, Dalby does not teach formulations comprising "crystalline drug particles", as required by Applicants' claims.

Further, Dalby teaches that "the micronized drug (e.g., BDP) should be easily dispersible in the propellant or propellant blend with the aid of the surfactant, or completely dissolve". Thus, Dalby does not teach formulations comprising

"nanoparticulate" drug particles, having an average particle size of less than 1 micron, as required by Applicants' claims.

2. Dalby Does Not Cure the Deficiencies of Edwards

For the reasons discussed above, Edwards does not teach or suggest the claimed aerosol compositions.

As Dalby does not teach or suggest: (1) crystalline drug particles; (2) component crystalline drug particles having an average particle size of less than about 1 micron; and (3) wherein the aggregates of nanoparticulate drug and surface modifier return to nanoparticulate drug particle dispersions upon reconstitution in a liquid medium, all of which are required by Applicants' claims, Dalby fails to fails to remedy the deficiencies of Edwards.

For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

D. Edwards in view of Goodman and Gilman's

Claims 120 and 121 stand rejected as being allegedly obvious over Edwards in view of Goodman and Gilman's ("Goodman"). Office Action at page 5. Applicants respectfully traverse this ground for rejection.

In maintaining this ground for rejection, the Examiner stated that "Goodman teaches aerosolized formulation of glucocorticoids for delivery by inhalation." Office Action at page 5.

This analysis fails to address whether Goodman remedies the deficiencies of Edwards, and whether Goodman provides motivation to modify the aerosol compositions of Edwards to obtain the claimed invention.

In fact, Goodman does not remedy the deficiencies of Edwards, nor does Goodman provide motivation to modify the compositions of Edwards to obtain the claimed invention. Specifically, Goodman does not address nanoparticulate crystalline drug compositions, spherically shaped aggregates of such compositions, or the

redispersion of such aggregates upon reconstitution in a liquid media, all of which are required by Applicants' claims. Thus, Goodman does not remedy the deficiencies of Edwards.

Accordingly, Applicants respectfully request withdrawal of this ground for rejection.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if he feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.